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An Effective Method of Cross-Mapping Between Different Biological Samples for Comprehensively Discovering *in Vivo* Metabolites of Herbal Medicines

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Commentary

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DESCRIPTION

The therapeutic effects of herbs usually attribute to their small molecular components. The exploration of herb-derived metabolites *in vivo* is very important for the elucidation of effectiveness mechanism, new drug discovery and development. However, the complex chemical constituents of herbs and their diverse metabolic pathways *in vivo* bring a major challenge for discovering the metabolites of herbal medicines. Recently, Liquid Chromatography with High Resolution Mass Spectrometer (LC-HRMS) has been widely used to identify the herb-derived metabolites due to its excellent resolution and superior sensitivity. Derived from the specific biogenic synthetic pathways and *in vivo* metabolic pathways, the herbal constituents and their metabolites share same backbones, with only minor differences in the substituents.

There are two main obstacles for the discovery and identification of metabolites. Firstly, the identification of herb-derived metabolites based on LC-HRMS relies mainly on standard compounds. The multi-component herbal system is transformed into more complicated herb-derived metabolites through a series of connected biochemical reactions. The collection of suitable standards is quite a difficult task. Secondly, complex matrices, low metabolite concentrations and limited Mass Spectrometry (MS)/Mass Spectrometry (MS) information acquisition in biological samples are barriers to the thorough detection and identification of herb-derived metabolites.

Aiming to tackle the two mentioned obstacles, we chose Yanhusuo as the vehicle. The strategies “representative compounds to herbal extract”,

"high dose to clinical dose" and the novel "cross-mapping between different biological samples" were integrated to explore approaches for discovering and identifying the herb-derived metabolites comprehensively. The "representative compounds to herbal extract" strategy is commonly implemented to screen and identify the *in vivo* metabolites of herbal medicines.

Firstly, representative compounds of a catalogue were selected for *in vivo* metabolic studies to predict the possible metabolic pathways. Second, data-mining methods are established based on the predicted metabolic pathways. The majority of prototype compounds and their metabolites may be screened out, and then the filtered metabolites are identified according to their characteristic fragments combined with polarity and retention time. The MS signals of Yanhusuo acquired from LC-HRMS were divided into two classes based on intensity. The stronger MS signals of Yanhusuo metabolites were identified by the "representative compounds to herbal extract" strategy.

The "high dose to clinical dose" strategy was used for the identification of the weaker MS signals. Structural identification of weaker MS signals was difficult because of the deficiency of MS/MS information. The enhancement of the dose could improve the intensity of the MS signal and the accuracy of structural identification. The stronger MS signals in high-dose samples were used as pseudo-standards to characterize weaker MS signals. In a separate report, the "high dose to clinical dose" strategy was also used to characterize *in vivo* metabolites of licorice at a normal clinical dosage systematically.

Interestingly, we observed that some metabolites were exist in different types of samples with different MS response. A reasonable explanation is that the differences in the distribution of drug-metabolizing enzymes in various tissues resulted in the differences in the types and levels of herb-derived metabolites. To break through the influence of the pathways and ability of biotransformation in different tissues or organs on the comprehensive exploration of drug metabolites, the "cross-mapping between different biological samples" strategy was proposed. The identified stronger MS signals in one biological sample were used to discover the complicated trace metabolite in another kind of biological sample. This strategy avoided tedious sample pretreatment process and improved the sensitivity of MS detection. In addition, various data mining strategies behind MS data acquiring, such as mass defect filtering, endogenous background subtraction, and computer-aided techniques and so on, were developed to improve the efficiency and accuracy of identification of herb-derived metabolites in biological systems. In this research, to enhance the efficiency of identification, the structure screening tables were established according to the type and number of substitutes and *in vivo* metabolic pathways. The metabolites of known prototype constituents could be widely predicted, which were applied to structural inference of drug metabolites.

Using the integrated strategy, 127 metabolites were detected and identified from rat biological samples. The integrated strategy improved the comprehensiveness of herb-derived metabolites and will be a powerful tool in the discovery of pharmacodynamic substances.

However, there are a large amounts isomers of drug metabolites that have not been elucidated. The structural differences result in significant differences in the pharmaceutical properties of active ingredients. It's a key step for the functional interpretation of pharmaceutical properties to clarify the structure of metabolites. Some isomers

could be initially distinguished by the characteristic fragment ions and the ClogP values. In fact, it is still a tough task to discriminate most position-isomers or stereo-isomers. To characterize the isomers more accurately, the QSRR model was established and applied to Phthalide compounds in Chuanxiong, and the phthalide isomers were explored in depth. In the future, Ion Mobility Mass Spectrometry (IM-MS) and more molecular descriptors, such as OCE and CE50, will be used in our experiments to explore the isomers.